II. REMARKS

Formal Matters

Claims 31, 35-38, 40, 41-47, 51, 52, 59, 60, 62, and 64 are pending after entry of the amendments set forth herein.

Claims 31, 35-38, 41-47, 51, 52, 59, 60, and 62 were examined and were rejected. Claims 40 and 64 were withdrawn from consideration.

Claims 31 and 60 are amended. The amendments to the claims were made solely in the interest of expediting prosecution, and are not to be construed as acquiescence to any objection or rejection of any claim. The amendments to claim 60 are editorial in nature; no new matter is added by the amendments to claim 60. Support for the amendments to claim 31 is found in the claims as originally filed, and throughout the specification, in particular at the following location: paragraph 00102. Accordingly, no new matter is added by the amendments to claim 31.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Withdrawn rejections

Applicants note with gratitude that the following rejections have been withdrawn:

1) rejection of claims 31, 35-38, 41-47, 51, 52, 55, 56, 59, 60, 62, 63, and 65 under 35 U.S.C. §112, second paragraph;
2) rejection of claims 31, 35-37, 56, 63, and 65 under 35 U.S.C. §102(b); and
3) rejection of claims 38, 41-47, 51, 52, 59, 60, and 62 under 35 U.S.C. §103(a).

Claim objection

The Office Action stated that claim 60 is objected to because the claim recites RNA transcripts that have not been elected.

Applicants elected Invention I in response to the Restriction Requirement dated December 23, 2005. The December 23, 2005 Restriction Requirement further required election of one of the genes listed in claim 60.

Applicants note that MPEP §803.04 states:

> **>Polynucleotide molecules defined by their nucleic acid sequence (hereinafter "nucleotide sequences") that encode< different proteins are structurally distinct chemical compounds**. These sequences are thus deemed to normally constitute independent and distinct inventions within the meaning of 35 U.S.C. 121. Absent evidence to the contrary, each such nucleotide sequence is presumed to represent an independent and distinct invention, subject to a restriction requirement pursuant to 35 U.S.C. 121and 37 CFR 1.141 *et seq.* Nevertheless, to further aid the biotechnology industry in protecting its intellectual property without creating an undue burden on the Office, the *>Director< has decided *sua sponte* to partially waive the requirements of 37 CFR 1.141 *et seq.* and

> permit a reasonable number of such nucleotide sequences to be claimed in a single application. See *Examination of Patent Applications Containing Nucleotide Sequences,* 1192 O.G. 68 (November 19, 1996).
> It has been determined that **normally ten sequences constitute a reasonable number for examination purposes**. Accordingly, in most cases, up to ten independent and distinct nucleotide sequences will be examined in a single application without restriction. (MPEP §803.04, emphasis added)

Claim 60 now recites "ErbB3; EREG; ID1; TITF1; CA9; CD44v6; DR5; KRT17; P14ARF; and PLAUR."

First, Applicants are not required to delete non-elected species from a dependent claim.

Secondly, claim 60 recites a reasonable number of sequences for examination purposes. As noted in the MPEP §803.04, normally ten sequences constitute a reasonable number of sequences for examination purposes. Claim 60 now recites ten RNA transcripts. As such, claim 60 recites a reasonable number of sequences. Thus, there is no need to delete any sequences from claim 60.

Rejection under 35 U.S.C. §112, first paragraph

Claims 31, 35-38, 41-47, 51, 52, 59, 60, and 62 were rejected under 35 U.S.C. §11, first paragraph, as allegedly failing to comply with the written description requirement.

The Office Action stated that the claims require a step of predicting the likelihood of response of the patient to treatment with an ErbB1 inhibitor based on the normalized level of LAMC2 transcript; and stated that the claim does not recite how one would use the LAMC2 level to make the prediction.

Without conceding as to the correctness of this rejection, claim 31 is amended to recite "wherein **an increased** normalized level of LAMC2 RNA transcript correlates with **resistance of the colon cancer** to treatment …."

The Office Action stated that claim 60 is broad because it recites a likelihood of response to treatment with any ErbB1 inhibitor.

Without conceding as to the correctness of this rejection, claim 60 is amended to recite "the ErbB1 inhibitor." Claim 60 depends from claim 31, which recites "wherein the ErbB1 inhibitor is erlotinib, cetuximab, or gefitinib."

The Office Action made various remarks regarding the teachings in the specification. Applicants' position has been made of record, e.g., in the amendment, filed on October 18, 2008 and responsive to the July 18, 2008 Office Action. Applicants previously explained the data provided in the specification, explained how normalized levels of predictive transcripts such as LAMC2 are used to predict likelihood of response to treatment with an ErbB1 inhibitor, and provided an expert Declaration further explaining these concepts. Applicants' position and explanations are therefore not reiterated here.

The Office Action asserted that the "unpredictability of correlating a gene expression level with an individual's response to treatment is taught in the post filing date art" and cited Evans ((2004) *Nature*; "Evans") and Lee et al. ((2005) *The Oncologist*; "Lee"). Office Action, page 7.

The Office Action stated that Evans "teaches that differences in DNA sequences that alter the expression of function of proteins that are targeted by drugs can contribute significantly to variation in responses of individuals." Office Action, page 7.

However, the Office Action has not presented any evidence that LAMC2, or any of the other predictive RNA transcripts discussed in the instant specification, is "targeted by drugs." As such, the cited teachings of Evans are not relevant to enablement of the instant claims.

The Office Action stated that Evans "teaches that although single gene defects can have a strong effect on their substrates, most of the phenotypic variability in drug response remains unexplained." Office Action, page 7.

However, the instant claims recite normalized levels of a predictive transcript, not "single gene defects." As such, the cited teachings of Evans are not relevant to enablement of the instant claims.

The Office Action stated that Lee "teaches that while genes likely contribute to the observed variability in cancer treatment outcome, there are several other variables that have been found to be associated with drug responses such as age, gender, diet, drug-drug interactions." Office Action, page 7.

However, the fact that other factors might contribute to variability in treatment outcome is irrelevant to the instant claims. The enablement requirement of 35 U.S.C. §112, first paragraph, does not require that Applicants recite every possible factor that might influence likelihood of patient response to cancer treatment. As such, the cited teachings of Lee are not relevant to enablement of the instant claims.

The Office Action stated that "the art of determining if erlotinib, cetuximib, and gefitinib will be less effective in patients with increased LAMC2 level is highly unpredictable." Office Action, page 7. The Office Action cited Giaccone and stated that Giaccone "teaches that EGFR inhibitors has a different mechanism in which it acts on EGFR receptor." Office Action, page 8. The Office Action concluded that "it is unpredictable as to whether the results obtained for colon cancer using whichever EGFR inhibitor the inventor used could be

extrapolated to other EGFR inhibitors because each inhibitor works by a different mechanism." Office Action, page 8.

As Applicants previously explained (see, e.g., the amendment, filed on October 18, 2008 and responsive to the July 18, 2008 Office Action), Applicants have shown a negative correlation between LAMC2 transcript levels and patient response to at least **three** classes of EGFR inhibitor, namely to:

1) EGFR inhibitors of the quinazoline class;

2) EGFR inhibitors of the monoclonal antibody class; and

3) EGFR inhibitors of the pyrrolopyrimidine class.

A number of ErbB1 inhibitor compounds of these and other classes were known in the art as of the November 15, 2002 priority date of the instant application; and the instant application lists several known ErbB1 inhibitors. Furthermore, it should be noted that **ligand-bound ErbB1 acts by activating certain well-known signaling pathways**. **It has been shown amply in the literature that these signaling pathways can be disrupted by any of a wide variety of ErbB1 inhibitors of a number of different classes**. As such, the possibility that various ErbB1 inhibitors might act by different mechanisms is irrelevant; the fact is that the recited ErbB1 inhibitors disrupt well-known pathways and the end result is inhibition. Thus, the cited teachings of Giaccone are irrelevant to enablement of the instant claims.

Conclusion as to the rejection under 35 U.S.C. §112, first paragraph

Applicants submit that the rejection of claims 31, 35-38, 41-47, 51, 52, 59, 60, and 62 under 35 U.S.C. §112, first paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number GHDX-005.

Respectfully submitted,
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Date: February 12, 2009

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